β4, TGF-β5, dpp, Vg-1, Vgr-1, 60A, BMP-2A, BMP-3, BMP-4, BMP-5, BMP-6, dorsalin, OP-1, OP-2, OP-3, GDF-1, GDF-3, GDF-9, Inhibin α, Inhibin βA and Inhibin βB.

21. (Added) The TGF-β family member fusion protein of claim 1, wherein the TGF-β family protein is selected from the group consisting of OP-1 and GDF-3.

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22. (Added) The TGF-β family member fusion protein of claim 1, wherein the TGF-β family protein is OP-1.

REMARKS

THE AMENDMENTS

Applicants have amended the specification at pages 2, 76 and 80 to insert the appropriate patent application numbers and filing dates thereof.

Applicants have amended the "Brief Description of the Drawings" to correct inadvertent typographical errors. The recitation of "hexa-histideine" in the brief description of Figure 7(J) was replace with "hexa-histidine". The recitation of "phosphotase" in the brief description of Figure 15 was replaced with "phosphatase".

Applicants have also amended the "Brief Description of the Drawings" to recite the SEQ ID NOs of the sequences presented in the figures.

Applicants have amended the specification at page 95 to recite a SEQ ID NO following the recited peptide.

Applicants submit herewith a substitute Sequence Listing. The substitute Sequence Listing differs from the original Sequence Listing in that it recites additional sequences (SEQ ID Nos: 89-124). These sequences correspond to the nucleotide and amino acid sequences recited in Figure 7(A)-(J) and 15. In

accordance with 37 C.F.R. § 1.821, applicants submit concurrently herewith a substitute Sequence Listing in computer readable form together with a Statement under 37 C.F.R. §§ 1.825(a) and (b) that the paper and computer readable copies of the substitute Sequence Listing are the same and do not include new matter.

Applicants have canceled claims 2-19. Applicants have canceled these claims without prejudice and without waiver of their right to file for and obtain claims directed to any non-elected subject matter in divisional and continuing applications which claim priority from this application.

Applicants have amended claim 1 to delete the recitation of "competent to refold under suitable refolding conditions". Applicants have also amended claim 1 to recite that the heterologous leader sequence domain is selected from the group consisting of a) a tissue-targeting domain which binds to a cell surface molecule on a chondrocyte, b) FB subdomain of staphylococcus aureus protein A, c) a peptide derived from Clostridium collagenase and d) a decapeptide collagen binding domain comprising amino acid residues 11-20 of SEQ ID NO.:89. Support for this amendment is provided at pages 77-78.

Applicants have added claims 20-22 to recite specific TGF-β superfamily member fusion proteins. Support for these claims can be found throughout the specification (see e.g., pages 14-16).

None of these amendments adds new matter.

Applicants now address the Examiner's objections and rejections.

THE OBJECTIONS

Specification

The Examiner has objected to the specification requesting correction of the blank spaces at pages 1*, 76 and 80 where U.S. patent application serial numbers are supposed to be.

Applicants have amended specification pages 2, 76 and 80 to insert the appropriate U.S. patent application serial numbers. Accordingly, the Examiner's objection has been obviated.

Sequence Identifiers

The Examiner has objected to the specification, stating that it is not in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the Examiner states that the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed.

Applicant has amended the specification to recite the appropriate sequence identifiers at each place where a sequence is discussed, thus, obviating the Examiner's objection.

THE REJECTIONS

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-5 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that it is unclear what is intended by "competent to refold under suitable refolding conditions" because the phrase

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* Applicants believe that the Examiner intended to recite page 2 rather than page 1.

"biologically active TGF-beta family member" presumes a correctly folded protein.

Applicants have canceled claims 2-5 and amended claim 1 to cancel the recitation of "competent to refold under suitable refolding conditions", thus, obviating the Examiner's rejection.

35 U.S.C. § 102(b)

The Examiner has rejected claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Hall, WO96/39430 ("Hall") in view of Suzuki et al. J. Dent Res. 77: 1799-1806 (1998) ("Suzuki"), Curiel, U.S. Publication US2002/0081280 ("Curiel") and Hruska, U.S. Patent 6,294,320 ("Hruska"). The Examiner contends that Hall teaches a transforming growth factor-β ("TGF-β") fusion protein, as well as a method of preparing and using the TGF-β fusion protein. The Examiner states that the TGF-β of Hall comprises a purification tag, at least one proteinase site, an extracellular matrix binding site, and a transforming growth factor active fragment. The Examiner states that Hall discloses ECM binding domains selective for collagen, fibronectin or a cell surface and that the ECM binding domain may be the RGD motif. The Examiner states that Suzuki teaches that bone is composed of type I collagen, that Curiel discloses that peptides containing the RGD motif bind αvβ3 integrin very efficiently and that Hruska discloses that αvβ3 integrin localizes in human osteoprogenitor cells. The Examiner, therefore, concludes that Hall teaches a biologically active TGF-β family member fusion protein that binds to a bone matrix protein and to a cell surface molecule on an osteoprogenitor cell.

Applicants traverse. The Examiner's reliance on Curiel and Hruska as evidence of the function of RGD motifs and the site of expression of αvβ3 integrin is

misplaced because both references were published well after the filing date of the instant application. However, to expedite prosecution, applicants have canceled claims 2-5 and amended claim 1 to recite a biologically active TGF-β family member fusion protein comprising a TGF-β family protein C-terminal seven cysteine domain and a heterologous leader sequence selected from the group consisting of a) a tissue-targeting domain which binds to a cell surface molecule on a chondrocyte, b) FB subdomain of *staphylococcus aureus* protein A, c) a peptide derived from *Clostridium* collagenase and d) a decapeptide collagen binding domain comprising amino acid residues 11-20 of SEQ ID NO.: 89. Hall does not disclose a TGF-β fusion protein as recited in the amended claims. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 102(e)

The Examiner has rejected claims 1-5 under 35 U.S.C. § 102(e) as being anticipated by Nimni, U.S. Patent 6,352,972 ("Nimni") in view of Curiel and Hruska. The Examiner contends that Nimni discloses a BMP-7 fusion protein comprising an extracellular matrix (ECM)binding site, wherein the ECM binding site is the RGD motif. The Examiner states that Curiel discloses that peptides containing the RGD motif bind αvβ3 integrin very efficiently and that Hruska discloses that αvβ3 integrin localizes in human osteoprogenitor cells. The Examiner therefore concludes that Nimni's BMP-7 fusion protein binds to a cell surface molecule on an osteoprogenitor cell. The Examiner further states that Nimni discloses binding domains which are selective for collagen, fibronectin or cell surface and that purification tags

such as $(His)_6$, which binds to hydroxyapatite of bone, may be used.

Applicants traverse. As stated above, the Examiner's reliance on post-filing references, Curiel and Hruska, to support his contention of the function of the RGD domain is misplaced. Curiel was published almost three years after the filing of the instant application and Hruska was published over two years after the filing of the instant application. However, as stated above, to expedite prosecution, applicants have canceled claims 2-5 and amended claim 1 to recite a biologically active TGF-β family member fusion protein comprising a TGF-β family protein C-terminal seven cysteine domain and a heterologous leader sequence selected from the group consisting of a) a tissue-targeting domain which binds to a cell surface molecule on a chondrocyte, b) FB subdomain of *staphylococcus aureus* protein A, c) a peptide derived from *Clostridium* collagenase and d) a decapeptide collagen binding domain comprising amino acid residues 11-20 of SEQ ID NO.: 89, which consists of a tissue targeting domain which binds to the cell surface of a chondrocyte. Nimni does not disclose a TGF-β fusion protein as recited in amended claim 1. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-5 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time the application was filed that applicants had possession of the claimed invention. The Examiner contends that the specification and claims do not indicate what distinguishing structural attributes

are shared by the members of the genus of targeting domains.

First applicants have canceled claims 2-5, thus, obviating the rejection with respect to those claims. Second, applicants have amended claim 1 to recite that the heterologous leader sequence is selected from the group consisting of a) a tissue-targeting domain which binds to a cell surface molecule on a chondrocyte, b) FB subdomain of *staphylococcus aureus* protein A, c) a peptide derived from *Clostridium* collagenase and d) a decapeptide collagen binding domain comprising amino acid residues 11-20 of SEQ ID NO.: 89. These domains are sufficiently described in the in the specification at pages 77-78. Accordingly, applicants request that the Examiner withdraw this rejection.

CONCLUSION

In view of the above, applicants request that the Examiner examine the pending claims in this application. Applicants request favorable consideration and early allowance of the pending claims.

Respectfully submitted,

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APPENDIX OF AMENDMENTS

IN THE SPECIFICATION

On page 2, replace the first full paragraph under "Continuing Application Data" with the following:

The instant utility application claims priority to U.S. provisional patent application number 60/103,418, filed on October 7, 1998, the entire contents of which is incorporated herein by reference; and the instant application is related to co-pending utility applications U.S.S.N.[_____] 09/374,958 and [_____] 09/374,936 (Attorney Docket Nos. STK-076 and STK-077) filed on even date herewith and also based on the aforementioned provisional application, the disclosures of which are incorporated herein by reference.

On page 24, replace the brief description of figure 4 with the following:

Figure 4 lists the aligned C-terminal residues defining the finger 2 sub-domain for various known members of the BMP family, and TGF-β superfamily of proteins, starting with the first residue following the cysteine doublet. OP-1 (amino acid residues 66-102 of SEQ ID NO: 55); BMP-5 (amino acid residues 66-102 of SEQ ID NO: 52); BMP-6 (amino acid residues 66-102 of SEQ ID NO: 53); OP-2 (amino acid residues 66-102 of SEQ ID NO: 56); OP-3 (amino acid residues 66-102 of SEQ ID NO: 57); 60A (amino acid residues 82-118 of SEQ ID NO: 48); Vg-1 (amino acid residues 66-102 of SEQ ID NO: 46); Univin (amino acid residues 1-35 of SEQ ID NO: 34); BMP-2 (amino acid residues 66-102 of SEQ ID NO: 49); BMP-4 (amino acid residues 65-101 of SEQ ID NO: 51); GDF-5 (amino acid residues 66-102 of SEQ ID NO: 83); GDF-6 (amino acid residues 66-102 of SEQ ID NO: 85); GDF-7 (amino acid

residues 66-102 of SEQ ID NO: 87); CDMP-2 (amino acid residues 66-102 of SEQ ID NO: 86); DPP (amino acid residues 66-102 of SEQ ID NO: 45); BMP-9 (amino acid residues 1-35 of SEQ ID NO: 7); Dorsalin (amino acid residues 66-103 of SEQ ID NO: 54); BMP-10 (amino acid residues 1-35 of SEQ ID NO: 8); GDF-3 (amino acid residues 65-101 of SEQ ID NO: 59); GDF-1 (amino acid residues 71-107 of SEQ ID NO: 58); SCREW (amino acid residues 1-35 of SEQ ID NO: 28); BMP-3 (amino acid residues 67-103 of SEQ ID NO: 50); NODAL (amino acid residues 1-34 of SEQ ID NO: 25); TGF-β1 (amino acid residues 63-98 of SEQ ID NO: 40); TGF-β2 (amino acid residues 63-98 of SEQ ID NO: 41); TGF-β3 (amino acid residues 63-98 of SEQ ID NO: 42); TGF-β4 (amino acid residues 63-98 of SEQ ID NO: 43); TGF-β5 (amino acid residues 63-98 of SEQ ID NO: 44); GDF-5 (amino acid residues 63-98 of SEQ ID NO: 40); Inhibin α (amino acid residues 66-105 of SEQ ID NO: 61); Inhibin βA (amino acid residues 70-106 of SEQ ID NO: 62); Inhibin βB (amino acid residues 70-106 of SEQ ID NO: 63); Inhibin βC (amino acid residues 1-35 of SEQ ID NO: 23); MIS (amino acid residues 1-34 of SEQ ID NO: 24); GDNF (amino acid residues 1-32 of SEQ ID NO: 19); BMP-11 (amino acid residues 1-35 of SEQ ID NO: 9); GDF-9 (amino acid residues 66-102 of SEQ ID NO: 60).

On page 25, replace the brief description of figure 5 with the following:

Figures 5A, 5B, and 5C are sequence alignments using single letter amino acid code, arranged to indicate alignments and homologies of the finger 1, heel, and finger 2 regions, respectively, of the currently known members of the TGF-β superfamily. Shown are the respective amino acids comprising each region of human TGF-β1 through TGF-β5 (the TGF-β subgroup), the Vg/dpp

subgroup consisting of dpp, Vg-1, Vgr-1, 60A (see copending U.S.S.N. 08/271,556), BMP-2A (also known in the literature as BMP-2), dorsalin, BMP-2B (also known in the literature as BMP-4), BMP-3, BMP-5, BMP-6, OP-1 (also known in the literature as BMP-7), OP-2 (see PCT/US91/07635 and U.S. Patent No. 5,266,683) and OP-3 (U.S.S.N 07/971,091), the GDF subgroup consisting of GDF-1, GDF-3, and GDF-9, the Inhibin subgroup consisting of Inhibin α, Inhibin βA, and Inhibin βB. The dashes (-) indicate a peptide bond between adjacent amino acids. A consensus sequence pattern for each subgroup is shown at the bottom of each subgroup. In Figure 5A the finger 1 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 1-34 of SEQ ID NO:40); TGF-β2 (residues 1-34 of SEQ ID NO:41); TGF-β3 (residues 1-34 of SEQ ID NO:42); TGF-β4 (residues 1-34 of SEQ ID NO:43); TGF-β5 (residues 1-34 of SEQ ID NO:44); TGF-β pattern (1-34 of SEQ ID NO: 64); dpp (residues 1-34 of SEQ ID NO:45); Vg-1 (residues 1-34 of SEQ ID NO:46); Vgr-1 (residues 1-34 of SEQ ID NO:47); 60A (residues 1-34 of SEQ ID NO:48); BMP-2A (residues 1-34 of SEQ ID NO:49); DORSALIN (residues 1-34 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 1-34 of SEQ ID NO: 51); BMP-3 (residues 1-34 of SEQ ID NO: 50); BMP-5 (residues 1-34 of SEQ ID NO:52); BMP-6 (residues 1-34 of SEQ ID NO:53); OP-1/BMP-7 (residues 1-34 of SEQ ID NO:55); OP-2 (residues 1-34 of SEQ ID NO:56); OP-3 (residues 1-34 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 1-34 of SEQ ID NO:65); GDF-1 (residues 1-34 of SEQ ID NO:58); GDF-3 (residues 1-34 of SEQ ID NO:59); GDF-9 (residues 1-34 of SEQ ID NO:60); GDF subgroup pattern (residues 1-34 of SEQ ID NO:66); Inhibin α (residues 1-34 of SEQ ID NO:61); Inhibin βA (residues 1-34 of SEQ ID NO:62); Inhibin βB (residues 1-34 of SEQ ID NO:63); Inhibin subgroup pattern (residues 1-34 of SEQ ID NO:67).

In Figure 5B the heel sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 35-64 of SEQ ID NO:40); TGF-β2 (residues 35-64 of SEQ ID NO:41); TGF-β3 (residues 35-64 of SEQ ID NO:42); TGF-β4 (residues 35-64 of SEQ ID NO:43); TGF-β5 (residues 35-64 of SEQ ID NO:44); TGF-β pattern (residues 35-64 of SEQ ID NO: 64); dpp (residues 35-67 of SEQ ID NO:45); Vg-1 (residues 35-67 of SEQ ID NO:46); Vgr-1 (residues 35-67 of SEQ ID NO:47); 60A (residues 35-67 of SEQ ID NO:48); BMP-2A (residues 35-66 of SEQ ID NO:49); DORSALIN (residues 35-67 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 35-66 of SEQ ID NO: 51); BMP-3 (residues 35-68 of SEQ ID NO: 50); BMP-5 (residues 35-67 of SEQ ID NO:52); BMP-6 (residues 35-67 of SEQ ID NO:53); OP-1/BMP-7 (residues 35-67 of SEQ ID 35-67 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 35-68 of SEQ ID NO:65); GDF-1 (residues 35-72 of SEQ ID NO:58); GDF-3 (residues 35-66 of SEQ ID NO:59); GDF-9 (residues 35-67 of SEQ ID NO:60); GDF subgroup pattern (residues 35-72 of SEQ ID NO:66); Inhibin α (residues 35-67 of SEQ ID NO:61); Inhibin βA (residues 35-71 of SEQ ID NO:62); Inhibin βB (residues 35-71 of SEQ ID NO:63); Inhibin subgroup pattern (residues 35-71 of SEQ ID NO:67).

In Figure 5C the finger 2 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 65-98 of SEQ ID NO:40); TGF-β2 (residues 65-98 of SEQ ID NO:41); TGF-β3 (residues 65-98 of SEQ ID NO:42); TGF-β4 (residues 65-98 of SEQ ID NO:43); TGF-β5 (residues 65-98 of SEQ ID NO:44); TGF-β pattern (residues 65-98 of SEQ ID NO: 64); dpp (residues 68-102 of SEQ ID NO:45); Vg-1 (residues 68-102 of SEQ ID NO:46); Vgr-1 (residues 68-102 of SEQ ID NO:47); 60A (residues 68-102 of SEQ ID NO:48); BMP-2A (residues 68-102 of SEQ ID NO:49); DORSALIN (residues 68-103 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 68-102 of SEQ ID NO: 51); BMP-3 (residues 68-102 of SEQ ID NO: 50);

BMP-5 (residues 68-102 of SEQ ID NO:52); BMP-6 (residues 68-102 of SEQ ID NO:53); OP-1/BMP-7 (residues 68-102 of SEQ ID NO:55); OP-2 (residues 68-102 of SEQ ID NO:56); OP-3 (residues 68-102 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 68-103 of SEQ ID NO:65); GDF-1 (residues 73-107 of SEQ ID NO:58); GDF-3 (residues 67-101 of SEQ ID NO:59); GDF-9 (residues 68-102 of SEQ ID NO:60); GDF subgroup pattern (residues 73-107 of SEQ ID NO:66); Inhibin α (residues 68-105 of SEQ ID NO:61); Inhibin βA (residues 72-106 of SEQ ID NO:62); Inhibin βB (residues 72-106 of SEQ ID NO:63); Inhibin subgroup pattern (residues 72-109 of SEQ ID NO:67).

On page 25, replace the brief description of figure 6 with the following:

Figure 6 is a single letter code listing of amino acid sequences, identified in capital letter in standard single letter amino acid code, and in lower case letters to identify groups of amino acids useful in that location, wherein the lower case letters stand for the amino acids indicated in accordance with the pattern definition key table set forth in Figure 3. Figure 6 identifies preferred pattern sequences for constituting the finger 1, heel, and finger 2 regions of biosynthetic constructs of the invention. The dashes (-) indicate a peptide bond between adjacent amino acids. The SEQ ID NOS for the subgroup patterns are as follows: TGF-β subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:64); TGF-β subgroup pattern heel (residues 35-64 of SEQ ID NO:64); TGF-β subgroup pattern finger 2 (residues 65-98 of SEQ ID NO:64); Vg/dpp subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:65); Vg/dpp subgroup pattern heel (residues 35-68 of SEQ ID NO:65); Vg/dpp subgroup pattern finger 2 (residues 69-104 of SEQ ID NO:65); GDF subgroup pattern finger 1 (residues 1-34 of SEQ ID

NO:66); GDF subgroup pattern heel (residues 35-72 of SEQ ID NO:66); GDF subgroup pattern finger 2 (residues 73-107 of SEQ ID NO:66); Inhibin subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:67); Inhibin subgroup pattern heel (residues 35-71 of SEQ ID NO:67); Inhibin subgroup pattern finger 2 (residues 72-109 of SEQ ID NO:67).

On pages 25-26, replace the brief description of figures 7A-J with the following:

Figure 7(A) shows the nucleotide (SEQ. ID NO: 90) and corresponding amino acid (SEQ. ID NO: 89) sequences of H2487, a modified OP-1 comprising N-terminal decapeptide collagen binding site inserted upstream of the seven-cysteine domain.

Figure 7(B) shows the nucleotide (SEQ ID NO: 92) and corresponding amino acid (SEQ. ID NO: 91) sequences of H2440, a modified OP-1 comprising a hexa-histidine domain attached 35 residues upstream of the first cysteine in the seven-cysteine domain.

Figure 7(C) shows the nucleotide (SEQ ID NO: 93) and amino acid (SEQ. ID NO: 94) sequences of H2521, a modified OP-1 comprising an FB leader domain of protein A attached 15 residues upstream of the first cysteine in the seven-cysteine domain.

Figure 7(D) shows the nucleotide (SEQ ID NO: 95) and amino acid (SEQ. ID NO: 96) sequences of H2525, a modified OP-1 comprising both an FB leader domain of protein A and a hexa-histidine domain.

Figure 7(E) shows the nucleotide (SEQ ID NO: 97) and amino acid (SEQ. ID NO: 98) sequences of H2527, a modified OP-1 comprising an FB leader domain, a hexa-histidine domain, and an ASP-PRO acid cleavage site.

Figure 7(F) shows the nucleotide (SEQ ID NO: 99) and amino acid (SEQ. ID NO: 100) sequences of H2528,

a modified CDMP-3 comprising an FB leader domain and a hexa-histidine domain.

Figure 7(G) shows the nucleotide (SEQ ID NO: 101) and amino acid (SEQ. ID NO: 102) sequences of H2469, a modified OP-1 (truncated) comprising 14 original residues upstream of the first cysteine in the conserved seven-cysteine domain.

Figure 7(H) shows the nucleotide (SEQ ID NO: 103) and amino acid (SEQ. ID NO: 104) sequences of H2510, a modified OP-1 comprising a collagen binding site inserted 7 residues upstream of the first cysteine in the conserved seven-cysteine domain.

Figure 7(I) shows the nucleotide (SEQ ID NO: 105) and amino acid (SEQ. ID NO: 106) sequences of H2523, a modified OP-1 comprising a collagen peptide and a spacer added 13 residues upstream from the first cysteine in the conserved seven-cysteine domain.

Figure 7(J) shows the nucleotide (SEQ ID NO: 107) and amino acid (SEQ. ID NO: 108) sequences of H2524, a modified OP-1 comprising a [hexa-histideine] hexa-histidine domain, a collagen peptide and a spacer added 13 residues upstream from the first cysteine in the conserved seven-cysteine domain.

On page 26, replace the brief description of figure 8 with the following:

Figure 8 is a restriction map encoding the OP-1 C-terminal seven cysteine active domain[;]. The DNA sequence corresponds to nucleotides 1036-1341 of SEQ ID NO: 38. The protein sequence corresponds to amino acid residues 330-431 of SEQ ID NO: 39.

On page 27, replace the brief description of figure 15 with the following:

Figure 15 shows the amino acid sequences for the finger 2 subdomain of various OP-1 mutants and their folding efficiencies and biological activities in the ROS cell based alkaline [phosphotase] phosphatase assay. OP-1 (residues 393-431 of SEQ ID NO: 39); 2421 (SEQ ID NO: 109); 2406 (SEQ ID NO: 110); 2410 (SEQ ID NO: 111); 2247 (SEQ ID NO: 112); 2234 (SEQ ID NO: 113); 2233 (SEQ ID NO: 114); 2418 (SEQ ID NO: 115); 2443 (SEQ ID NO: 116); 2447 (SEQ ID NO: 117); 2457 (SEQ ID NO: 118); 2456 (SEQ ID NO: 119); 2460 (SEQ ID NO: 120); 2449 (SEQ ID NO: 121); 2467 (SEQ ID NO: 122) and 2464 (SEQ ID NO: 123).

On page 76, replace the last paragraph with the following:

The mutant proteins of the present invention exhibit improved biological activity as well as extended half-life. Further, increased activity observed with the truncated proteins of the present invention may be due to elimination of basic residues and/or the lowering of the protein's isoelectric point. Biological activity and improved refolding can be enhanced when the modified proteins of the present invention are combined with the modifications described in copending applications [Atty Docket No. STK-076, USSN 09/374,958, filed on [_____] August 16, 1999] and [Atty Docket No. STK-077, USSN 09/374,936, filed on [_____] August 16, 1999], the disclosures of which are incorporated herein by reference.

On page 80, replace the first full paragraph with the following:

E.coli expression for construction of heterodimers of the present invention is preferred, because the practitioner can adjust the ratio of each monomer for optimal yields of heterodimer. In addition, this method is very rapid. For example, in an *in vitro*

heterodimer formation experiment between the hexa-histidine tagged OP-1, modified with the preferred modifications of charged amino acids, E, D, E, and R, (H2440) (see, for example, Attorney Docket No. STK-076, USSN 09/374,958 [_____], the entire disclosure of which is incorporated by reference herein) and BMP-2, the yield of heterodimers were excellent. There is an exceptionally high yield of heterodimer, more than the theoretically expected 50% heterodimer and 25% of each homodimer. This may occur because BMP-2 associates more readily with OP-1 than with itself, or faster than OP-1 reassociates with itself. Alternatively, the BMP-2 may act as chaperone for folding. Another experiment also showed heterodimer formation between BMP-2 and the H2447 mutant, OP-1 (no hexa-his tag), which also associated readily, generating good yields of heterodimer. Heterodimers were also made between FB-OP-1 (H2521) and BMP-2. Heterodimers of truncated OP-1, H2469 (retaining 15 residues upstream of the first cysteine), and BMP-5 (H2475); and H2469 and CDMP-2 (H2471) have also been constructed.

On page 95, replace the paragraph immediately after the heading "EXAMPLE 9. Activity of 'domain swapping' mutant" with the following:

Domain swapping occurs, for example, when one takes the N-terminal region of one type of TGF-β family member protein and attaches it to the seven cysteine domain of another type of TGF-β family member protein. A mutant construct was created by splicing the sequence of the BMP-2 terminus onto the seven cysteine active domain of OP-1 using routine techniques generally known to those of ordinary skill in the art. The resulting mutant, H2549, has an N-terminal region consisting of

MQAKHKQRKRLKSS-C (SEQ ID NO: 124). The last amino acid, cysteine, is the first cysteine of the seven cysteine active domain of OP-1. A ROS assay, as described above in Example 5, was used to test activity of H2549.

IN THE CLAIMS

1. (Amended) A biologically active TGF-β family member fusion protein [competent to refold under suitable refolding conditions], comprising:

a TGF-β family protein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and

a heterologous leader sequence domain operatively linked to said C-terminal domain; wherein said heterologous leader sequence domain is selected from the group consisting of

a) a tissue-targeting domain which binds to a cell surface molecule on a chondrocyte,

b) FB subdomain of staphylococcus aureus protein A,

c) a peptide derived from Clostridium collagenase and

d) a decapeptide collagen binding domain comprising amino acid residues 11-20 of SEQ ID NO.:89.

20. (Added) The TGF-β family member fusion protein of claim 1, wherein the TGF-β family protein is selected from the group consisting of TGF-β1, TGF-β2, TGF-β3, TGF-β4, TGF-β5, dpp, Vg-1, Vgr-1 60A, BMP-2A, BMP-3, BMP-4, BMP-5, BMP-6, dorsalin, OP-1, OP-2, OP-3, GDF-1, GDF-3, GDF-9, Inhibin α, Inhibin βA and Inhibin βB.

21. (Added) The TGF-β family member fusion protein of claim 1, wherein the TGF-β family protein is selected from the group consisting of OP-1 and GDF-3.

22. (Added) The TGF-β family member fusion protein of claim 1, wherein the TGF-β family protein is OP-1.